#8 GD 4/29/03

Attorney's Docket No. 04035.244910

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	Raschke et al.		
Appl. No.:	10/090,493	Group Art Unit:	1615
Filed:	March 4, 2002	Confirmation No.:	6041
For:	ACTIVE INGREDIENT COMBINATIONS OF SURFACE-ACTIVE CITRIC ESTERS AND INCLUSION COMPOUNDS OF CYCLODEXTRINS AND RETINOIDS, AND COSMETIC AND DERMATOLOGICAL PREPARATIONS CONTAINING SUCH MIXTURES		

March 24, 2003

Assistant Commissioner for Patents
Washington, DC 20231

RULE 132 DECLARATION OF Thomas Raschke

Sir:

I, Thomas Raschke, do hereby declare and state as follows:

1. I am a co-inventor of the invention described and claimed in the above-referenced patent application. I have reviewed the Office Action mailed October 22, 2002, and the documents cited therein.

2. I conducted the following test to compare the stability of a retinoid in a composition including a glyceride and saturated fatty acid ester, partially neutralized with citric acid, as an emulsifier, as compared to a composition including the same retinoid but a different emulsifier. Specifically, the stability of a retinol-γ-cyclodextrin complex in a composition that includes glyceryl stearate citrate as an emulsifier was compared to the stability of the same retinol-γ-cyclodextrin complex in a composition that includes glyceryl stearate as an emulsifier.

3. The following compositions were prepared and tested:

Example 1 (invention)

O/W-Crème

	Weight -%
Glyceryl stearate citrate	2,00
Stearyl alcohol	5,00
Caprylic /Capric triglyceride	3,00
Octyldodecanol	3,00
Dicaprylylether	3,00
Hydrogenated Coco-glycerides	3,00
Glycerin	3,00
Carbomer	0,10
Retinol (γ-cyclodextrin complex [1:2])	0,44
Preservatives	q.s.
Sodium hydroxide	q.s.
Perfume	q.s.
Water	ad 100,00

Preparation procedure:

The oily and the aqueous phase are heated separately to 75°C. Then both phases are combined under intensive stirring with a propeller stirrer for ca. 5 minutes. After addition of the active agent retinol-cyclodextrin (CD) complex, the hot preemulsion (containing also the carbomer and the preservatives) is placed into a high shear homogeniser (Type FZ 100L1, manufacturer: Zehnder AG, Zürich, Switzerland) for ca. 2 minutes. This warm emulsion is allowed to cool down to room temperature under gentle stirring. The perfume is added at ca. 40°C. After stirring for ca. 30 min at room temperature, the emulsion is placed into the above mentioned high shear homogeniser a second time, giving the completed emulsion.

Example 2 (comparative)

O/W-Crème

	Weight -%
Glyceryl stearate	6,50
Cetylalcohol	2,00
Caprylic /capric triglyceride	7,00
Squalane	1,00
Dicaprylylether	2,00
Cyclometicone	2,00
Cetearyl Isononanoate	2,00
Glycerin	13,00
Retinol (γ-cyclodextrin complex [1:2])	0,19
Tocopheryl acetate	2,00
Mg-Ascorbyl phosphate	0,10
Preservatives	q.s.
Na-Pyrrolidone carboxylic acid	2,00
Carbomer	0,15
Sodium hydroxide	q.s.
Perfume	q.s.
Water	ad 100,00

Preparation procedure:

The oily and the aqueous phase are heated separately to 75°C. Then both phases are combined under intensive stirring with a propeller stirrer for ca. 5 minutes. After addition of the active agent retinol-cyclodextrin (CD) complex, the hot preemulsion (containing also the carbomer and the preservatives) is placed into a high shear homogeniser (Type FZ 100L1, manufacturer: Zehnder AG, Zürich, Switzerland) for ca. 2 minutes. This warm emulsion is allowed to cool down to room temperature under gentle

stirring. The perfume and the other actives (Mg-Ascorbyl phosphate, Tocopheryl acetate, Na-Pyrrolidone carboxylic acid) are added at ca. 40°C. After stirring for ca. 30 min at room temperature, the emulsion is placed into the above mentioned high shear homogeniser a second time, giving the completed emulsion.

The activity stability of the retinoid complex of each composition is determined using HPLC-analytics (Merck-Hitachi System with DAD). Since the retinol forms relatively strong complexes with γ-cyclodextrin it is important to thoroughly extract the uncomplexed retinol from the emulsion matrix with an suitable solvent (eg. dimethylformamide) before HPLC analysis in order to avoid loss of retinol by uncomplete extraction.

The results are shown in the Table below.

	System	Recovery (activity) 3 month room temperature	Recovery (activity) 3 month 40°C
Example 1	Retinol-CD complex Glyceryl stearate citrate	91%	89%
Example 2	Retinol-CD complex Glyceryl stearate	50%	42%

The results demonstrate that the emulsion system of the invention is superior with regard to retinoid stability as compared to an emulsion system using a different emulsifier.

4. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

March, 24, 2003 Thomas Raschke

Date

CLT01/4581954v1